REMARKS

I. Amendments

Claims 1-4, 10, 16, 30, 36 and 37 were withdrawn, claims 5-9, 11-15, 17-19, 31-35, 38, 51 and 52 were canceled, and claim 39 has been amended. Upon entry of the amendment, claims 39-50 will be pending. The amendment does not constitute new matter and is supported throughout the specification, for example, on page 6, lines 24-29.

II. Rejections

A. Rejections under 35 U.S.C. § 101

Claims 39-52 stand rejected as the claimed invention allegedly is not supported by either a specific or substantial asserted utility or a well-established utility. The claims as amended are drawn to a transgenic mouse whose genome comprises a homozygous disruption in a gene encoding mCAR2, wherein as a result of the disruption, the transgenic mouse lacks production of functional protein encoded by said gene and exhibits, relative to a wild-type mouse, impaired coordination or balance, a spleen abnormality, a thymus abnormality or a lymph node abnormality. The Examiner essentially argues that: (i) studying the mouse to determine the function of a gene is not in and of itself a substantial utility (page 8); and (ii) none of the phenotypes correlate to a useful phenotype because the phenotypes described are not specific to a disease and are not linked to a disruption in the human equivalent of SQ ID NO:1 (page 4).

Applicant respectfully disagrees.

According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.
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> . . .
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> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion

would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)). Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has either a well-established utility or is useful for a particular practical purpose. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined. According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
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> . . .
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> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834) (emphasis added). Thus, the knockout mouse has been accepted as one of the premier models for determining gene function, a utility that is specific, substantial and credible.

Commercial use and acceptance is one important indication that the utility of an invention has been recognized by one of skill in the art ("A patent system must be related to the world of commerce rather than to the realm of philosophy." *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)). Commercial use of the knockout mice produced by Assignee Deltagen has been clearly established. Deltagen has created a database comprising characteristics derived from approximately 750 lines of knockout mice. Three of the largest pharmaceutical companies in the world, Merck, Pfizer and GSK, have subscribed to the database and requested access to the lines of mice for the purpose of studying gene function. In fact, six (6) commercial and academic institutions, including Merck, Pfizer and GSK, have ordered the presently claimed mCAR2 knockout mouse. This commercial acceptance more than satisfies the practical utility requirement of section 101.

Applicant respectfully submits that this is not a case where the sole asserted utility is as an object of use-testing (*See, Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966); "We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product"). The dicta in *Brenner* related to the patentability of a chemical compound which itself had no known use. The Court opined that the utility could not solely consist of testing the compound in order to determine a utility for the compound itself. In contrast, the mCAR2 knockout mouse is useful for the study of the utility and function of the mCAR2 gene, and not for the purpose of establishing a utility for the mouse. The practical distinction is clear: one skilled in the art would not understand what to do with a compound without a defined use, but would immediately recognize the use of a knockout mouse having a specific gene disruption.

Knockout mice may be appropriately analogized to other research tools, with respect to which the Patent Office has commented:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the

> setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). The use of knockout mice as research tools is recognized by those skilled in the art. For example, according to Crabbe *et al.* (Science (1999) 284:1670-1672) *a reference cited by the Examiner*), "[t]argeted and chemically induced mutations in mice are valuable tools in biomedical research." As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function).

The role of knockout mice in studying the function of orphan nuclear hormone receptors is well-established. For example, Luo *et. al.* (*J Steroid Biochem Mol Biol.* 1999, 69(1-6):13-8) generated a transgenic mouse having a disruption in SF-1, an orphan nuclear hormone receptor:

> Steroidogenic factor 1 (SF-1), an orphan nuclear receptor, initially was isolated as a key regulator of the tissue-specific expression of the cytochrome P450 steroid hydroxylases. Thereafter, analyses of sites of SF-1 expression during mouse embryological development hinted at considerably expanded roles for SF-1, roles that were strikingly confirmed through the analyses of SF-1 knockout mice. These SF-1 knockout mice exhibited adrenal and gonadal agenesis, associated with male-to-female sex reversal of their internal and external genitalia and death from adrenocortical insufficiency. These findings showed unequivocally that SF-1 is essential for the embryonic survival of the primary steroidogenic organs. SF-1 knockout mice also had impaired pituitary expression of gonadotropins and agenesis of the ventromedial hypothalamic nucleus (VMH), establishing that SF-1 regulates reproductive function at all three levels of the hypothalamic-pituitary gonadal axis.

(abstract). By way of further example, Choi *et al.* (*Genes Dev.* (1994) 8(20):2466-77) produced a transgenic mouse have a deficiency in HFN-4, another orphan nuclear hormone receptor:

> Expression of HNF-4, a transcription factor in the steroid hormone receptor superfamily, is detected only in the visceral endoderm of mouse embryos during gastrulation and is

> expressed in certain embryonic tissues from 8.5 days of gestation. To examine the role of HNF-4 during embryonic development, we disrupted the gene in embryonic stem cells and found that the homozygous loss of functional HNF-4 protein was an embryonic lethal. Cell death was evident in the embryonic ectoderm at 6.5 days when these cells normally initiate gastrulation. As assessed by expression of Brachyury and HNF-3 beta, primitive streak formation and initial differentiation of mesoderm do occur, but with a delay of approximately 24 h. Development of embryonic structures is severely impaired. These results demonstrate that the expression of HNF-4 in the visceral endoderm is essential for embryonic ectoderm survival and normal gastrulation.

(abstract). Both of these example illustrate that knockout mice are widely used to study gene function.

Finally, Applicant notes that in an Office Action dated November 20, 1993, the Examiner rejected the claimed invention as obvious under section 103. The Examiner argued: "[o]ne of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the nuclear hormone receptor gene instead of the gene disrupted by Capecchi to determine the function of the nuclear hormone receptor of SEQ ID NO:1 *in vivo*." (p. 10). Thus, while the Examiner argued that one skilled in the art would have been motivated to make the Applicant's claimed mouse, he also argues that one skilled in the art would not know how to use such a mouse once created. Applicant submits that the Examiner's previous statements are an admission that the present invention has a well-established utility, i.e., determining the function of a gene.

Applicant submits that since one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, a utility that is specific, substantial and credible, the invention has a well-established utility, thus satisfying the utility requirement of section 101. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

In addition, the claimed invention is useful for a particular purpose. The Applicant has demonstrated and disclosed specific phenotypes of the presently claimed mice, i.e., impaired coordination and balance, a spleen abnormality, a thymus abnormality and a lymph node abnormality. Utility of a knockout mouse demonstrating any of these properties would be apparent to, and considered credible by, one of skill in the art.

The Examiner argues that none of the phenotypes correlate to a useful phenotype because the phenotypes described are not specific to a disease and are not linked to a disruption in the human equivalent of SEQ ID No:1.

Applicant respectfully disagrees. The Examiner's arguments are similar to arguments made by the Patent Office with respect to pharmaceutical compounds the utility of which were based on murine model data, arguments which were dismissed by the Federal Circuit in *In re Brana* (34 U.S.P.Q.2d 1436)(Fed. Cir. 1995). The case involved compounds that were disclosed to be effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The court ruled that the PTO had improperly rejected, for lack of utility, claims for pharmaceutical compounds used in cancer treatment in humans, since neither the nature of invention nor evidence proferred by the PTO would cause one of ordinary skill in art to reasonably doubt the asserted utility.

The first basis for the Board's holding of lack of utility (the Board adopted the examiner's reasoning without any additional independent analysis) was that the specification failed to describe any specific disease against which the claimed compounds were useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. (*In re Brana* at 1439-40). The Federal Circuit reasoned that the leukemia cell lines were originally derived from lymphocytic leukemias in mice and therefore represented actual specific lymphocytic tumors. The court concluded that the mouse tumor models represented a specific disease against which the claimed compounds were alleged to be effective. (*In re Brana* at 1440).

The Board's second basis was that even if the specification did allege a specific use, the applicants failed to prove that the claimed compounds were useful.

The Federal Circuit responded: "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (*Brana* at 1441, *citing In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)). From this it followed that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO

provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. (*Id.*)

The court held that the Patent Office had not met its burden. The references cited by the Board did not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, the references merely discussed the therapeutic predictive value of *in vivo* murine tests -- relevant only if the applicants were required to prove the ultimate value in humans of their asserted utility. The court did not find that the nature of the invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. The purpose of treating cancer with chemical compounds did not suggest an inherently unbelievable undertaking or involve implausible scientific principles. (*Id.*)

The Court concluded that one skilled in the art would be without basis to reasonably doubt the asserted utility on its face. The PTO had not satisfied its initial burden. Accordingly, the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. (*Id.*)

As in *Brana*, Applicant has asserted that the claimed invention is useful for a particular practical purpose, an assertion that would be considered credible by a person of ordinary skill in the art. For example, the mCAR2 deficient mice have demonstrated impaired coordination and balance, and abnormalities in the spleen, thymus and lymph nodes. Based on these phenotypes, the mice demonstrate a role for the mCAR2 gene in physiological development. They would be useful in further study in the field of developmental biology. The mice also demonstrate a role for the gene in motor coordination, thus serving a use for further study in the field of neuroscience. It is also possible that these abnormalities in human may be associated with mutations in hCAR. Thus, such mice are useful for studying whether such conditions in humans are associated with the human CAR2 gene and for developing treatment strategies and therapeutics associated with any such mutations. The mice may also be useful in drug development strategies where, for example, they can be used as controls to determine the effectiveness or specificity of putative agents that target the mCAR or hCAR gene or its expression product by comparing the animal's physiological response to that of a wild-type animal.

That the specification does disclose a link between these particular phenotypes and the gene in mice and humans does not detract from the utility of the mice. In *Brana*, the claimed compound had demonstrated activity against a murine tumor implanted in a mouse. Yet, the Federal Circuit found that utility had been demonstrated. Here, the invention relates to a disruption to a murine gene in a mouse. Like the tumor mouse model, the knockout mouse with a specific gene disrupted is a widely accepted model, the utility of which would be readily accepted in the art. It is submitted that one skilled in the art would be without basis to be reasonably doubt Applicant's asserted utility, and therefore the Examiner has not satisfied his initial burden.

It is respectfully submitted that the Examiner needs to assess utility in light of the nature of the invention. Applicant is claiming a knockout mouse. The burden should not be placed on Applicant to establish that hCAR mutations in humans result in the same phenotypes observed in mice. This task is more appropriately placed on the commercial and academic entities conducting further research using the present invention. As noted by the Federal Circuit, usefulness in patent law necessarily includes the expectation of further research and development. (*In re Brana* at 1442).

In summary, Applicant submits that the claimed mCAR2 knockout mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the mCAR2 gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the specific phenotypes of the transgenic mice demonstrate that the mice are useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly established a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant would be specific and substantial. (*In re Brana*; MPEP § 2107). Withdrawal of the rejections is therefore respectfully requested.

B. Rejections under 35 U.S.C. § 112, 1st para.

Claims 39-52 stand rejected as failing to comply with the written description requirement. The Examiner argues that "mCAR gene" recited in claim 39 is new matter. Claim 39 has been amended to recite "mCAR2."

The Examiner argues that claim 51 recital of "tissue" is new matter. Claim 51 has been canceled.

Withdrawal of the rejections is respectfully requested.

C. Rejections under 35 U.S.C. § 112, 2nd para.

Claims 39-52 have been rejected as being indefinite. The Examiner argues that the metes and bounds of "mCAR gene" recited in claim 39 cannot be determined. Claim 39 has been amended to recite "mCAR2." Withdrawal of the rejection is respectfully requested.

It is submitted that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 13-2725.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

9-3-04
Date

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